Remarks

Reconsideration and withdrawal of the rejections set forth in the Office Action dated December 18, 2002 are respectfully requested. Applicants petition the Commissioner for a 3-month extension of time: a separate petition accompanies this amendment.

I. Amendments

Claims 9-15, 17 and 18 stand cancelled.

Claim 1 is amended to clarify that the present invention is a method for entrapping a supersaturated compound solution in liposomes and to set forth the steps required for accomplishing the method.

Claim 5 is amended to recite liposome size intervals between about 70 nm and about 500 nm. Support for this amendment can be found on page 8, lines 13-14.

Claims 6, 8, and 9 are amended for consistent terminology with claim 1.

Claim 16 is amended for clarity and grammar.

II. Rejections under 35 U.S.C. §112, second paragraph

Claims 1, 3-9, and 16 are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. These rejections are respectfully traversed. The Examiner had four specific objections, which are set forth and addressed below.

The court has consistently stated that claim language must be read in light of prior art and teachings of the specification. The standard is that the "definiteness of the language must be analyzed...in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary level of skill in the pertinent art." *In re Moore*, 439 F.2d 1232, 169 USPQ 236 (CCPA 1971). A claim which is clear to one ordinarily skilled in the art when read in light of the

specification, does not fail for indefiniteness. *Slimfold Mfg. Co. v. Kinkead Indus., Inc.*, 932 F2d 1453, 1 USPQ2d 1536 (Fed. Cir 1986).

1. Rejection of Claim 1: The Examiner objected to the claim as claiming a specific method of preparation of liposomes, but allegedly not reciting the individual steps.

Claim 1 is amended to recite a "method of entrapping a supersaturated compound solution in liposomes." In brief, the method involves the steps of (1) selecting a compound; (2) providing a supersaturated solution of the compound; (3) selecting a liposome size which inhibits precipitation of the compound from the supersaturated solution when entrapped in liposomes; and (4) forming liposomes of the selected size and which contain the supersaturated solution of the compound.

Each of these steps would be clear to one of skill in the art, based on that person's knowledge of the art and from a reading of the specification. Specifically, one of skill in the liposome art can easily perform steps (1), (2), and (4): select a compound, provide a supersaturated solution of the compound, and form liposomes. Based on the teachings in the specification at page 8, lines 2-29, one of skill can conduct step (3): selecting a liposome size which inhibits precipitation of the compound from the supersaturated solution when entrapped in liposomes. Since the claim would be clear to one of skill in the art, the claim complies with the definiteness requirement of 35 U.S.C. §112, second paragraph.

2. Rejection of Claims 1 and 16: The Examiner objected to the claims as not reciting how the supersaturated solution of the compound is entrapped in the liposomes.

Applicants submit that methods of entrapping a compound in liposomes is well known to one skilled in the art. Applicants further direct the Examiner to page 2, lines 6-14 for an exemplary method of entrapping a compound in a liposome and to Example 1 on page 22 where preparation of an exemplary composition is detailed.

3. Rejection of Claims 1, and 3-9: The Examiner questioned how the size of the liposomes by itself would not cause precipitation of the compound. Further, the Examiner questions how the size is selected.

Although an Applicant is not required to understand how or why an invention works (*In re Spada*, 911 F2d 705, 15 USPQ2d 1655 (Fed. Cir. 1990)), Applicants respectfully direct the Examiner to page 22, lines 7-15 for one possible explanation for how the size of the liposomes prevents precipitation or crystallization of the supersaturated solution.

With regard to how the size is selected, Applicants respectfully direct the Examiner to page 8, lines 2-9 for a listing of exemplary methods of selecting an liposome size including sonication, homogenization and extrusion. Applicants further direct the Examiner to page 23, lines 18-21 where liposomes are sized by the controlled extrusion method.

4. Rejection of Claim 16: The Examiner objected to the language "concentrated" as allegedly indefinite.

Although Applicants define the term "concentrated" as used with reference to the present invention on page 6, lines 16-19, Applicants have amended the claim to recite a "supersaturated solution" to ease examination.

Applicants submit that the claims are clear, when read in light of the prior art and teachings of the specification. In view of the foregoing, Applicants respectfully request that the rejections under 35 U.S.C. §112, second paragraph be withdrawn.

III. Rejections under 35 U.S.C. §102

Claims 1, 3-6, 11-13, and 15-17 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Mezel (EP Patent No. 0 177 223).

Claims 1, 3-6, 8-9, 11-13, 15-17 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Yamamoto, *et al.* (EP Patent No. 0 551 169).

Claims 1, 3-9, 11-18 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Abra *et al.* (PCT Publication No. WO 98/07409).

These rejections are respectfully traversed.

A. The Present Invention

The present invention describes a method for entrapping a supersaturated solution of a compound in a liposome. The method comprises (i) selecting a compound having room temperature water solubility capable of exhibiting at least a two-fold increase in response to a condition selected from (a) increasing solvent temperature, (b) adding a co-solvent, and (c) changing the solvent pH, (ii) providing an aqueous supersaturated solution of the compound, (iii) selecting a liposome size which is effective to inhibit precipitation of the compound in the supersaturated solution when entrapped in the liposome, and (iv) forming liposomes having the selected size and which contain the supersatured solution of the compound.

B. The Cited Art

MEZEL relates to a pharmaceutical multi-phase composition for use as a drug delivery system. The system is described as a "multi-component" system (page 7, lines 6-9). This includes, for example, an active ingredient that is present in "two" states in the invention, *i.e.*, in solution and in solid form within and outside the lipid vesicles (page 7, lines 9-11). The biologically active agent is dispersed in the product in (a) liposome encapsulated form; (b) in super-saturated solution form; and (c) in solid form. The liposomes of Mezel are spherical shaped liposomes of various sizes between 1-15 μm (page 12, lines 8-10).

YAMAMOTO ET AL. relate to a liposome composition in which a water-soluble drug is encapsulated in high concentration within liposomes (col. 1, lines 3-6). It is described

that when a drug in liposomes is present in the supersaturated state or in the form of solids or crystals, the amount of the drug per unit lipid amount can be increased (col. 2, lines 20-24).

ABRA ET AL. relate to a liposomal composition containing an entrapped cisplatin compound (page 1, lines 6-7): In one embodiment, the aqueous cisplatin solution is heated to a temperature sufficient to achieve a two-fold increase in cisplatin solubility over its room temperature solubility (page 3, lines 12-14). The drug is entrapped in the inner aqueous compartment in dissolved or precipitated form (page 4, lines 34-35).

C. Analysis

1. Legal Standard

The standard for lack of novelty, that is, for anticipation, is one of strict identity. To anticipate a claim for a patent, a single prior source must contain all its essential elements. M.P.E.P. § 2131.

2. Analysis of Rejection over Mezel

Claims 1 and 16 of the present invention require providing "a supersatured solution of the compound." A "supersaturated solution" is understood, based on the teachings in the specification and as commonly understood in the art, to refer to a solution that holds more of a dissolved solute than is required to produce equilibrium with its undissolved solute (page 6, lines 7-10). That is, the supersaturated solution contains solute in dissolved form. Claims 1 and 16 further require forming liposomes of a size that is effective to inhibit precipitation of the compound from the supersaturated solution when the supersaturated solution is contained within the liposomes.

Mezel fails to teach these elements of the present invention. The multi-phase composition of Mezel is present in "two" states, in solution and in solid form. As such, the multi-phase composition of Mezel would not be a supersaturated solution, due to the presence of the solid material. Presence of the solid form of the compound in the

supersaturated solution of Mezel results in "seeding" of the solution and formation of precipitate. In contrast, the present claims are directed to liposomes where the compound is entrapped in the form of a supersatured solution with no precipitate.

Accordingly, since Mezel fails to teach every element of the invention as claims, withdrawal of the rejection is respectfully requested.

3. Analysis of Rejection over Yamamoto *et al.*

As noted above, the size of the liposomes of the present invention are selected to inhibit precipitation of the compound from the supersatured solution, so that no precipitate is present in the liposome.

Nowhere does Yamamoto *et al.* teach selection of liposome size in order to maintain the compound in the form of a supersatured solution. Yamamoto *et al.* teach formation of liposomes from a supersaturated drug solution. The supersaturated state is maintained during liposome formation via increased temperature (page 4, lnes 25-33). After liposome formation, the liposome solution is cooled, to recover unentrapped drug in the form of precipitate (see Example 1). Yamamoto *et al.* state that the drug concentration in liposomes at the time of their formation is about the same as that in the external phase (page 4, lines 34-36), so presumably the drug entrapped in the liposomes precipitates simultaneous with the temperature cooling done to recover the unentrapped drug. This presumption is supported by the teaching in Yamamoto *et al.* that the drug is entrapped in the liposomes in the "supersatured state or in the form of solid or crystals" (page 2, lines 21-23; emphasis added). It is noteworthy that Yamamoto *et al.* describe the drug as entrapped in a supersaturated "state", as opposed to a supersatured "solution" as presently claimed. In any case, Yamamoto *et al.* nowhere teach a step of selecting a liposome size effective to inhibit precipitation of the compound from the supersatured solution when entrapped in the liposomes. Thus, withdrawal of the rejection is respectfully requested.

4. Analysis of Rejection over Abra *et al.*

Abra *et al.* fail to teach teach selection of liposome size in order to maintain the compound in the form of a supersatured solution. The liposomal composition of Abra *et al.* contains an entrapped cisplatin compound in "dissolved or precipitated form" (page 4, lines 34-35). Abra *et al.* nowhere mention a liposome entrapped compound in the form of a supersaturated solution.

Accordingly, Applicants submit that standard of strict identity to maintain a rejection under 35 U.S.C. § 102 has not been met. Withdrawal of the rejections under 35 U.S.C. §102(b) is respectfully requested.

IV. Rejections under 35 U.S.C. §103

Claims 7, 14, and 18 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over either of Mezel or Yamamoto *et al.* in combination with Woodle *et al.* (US Patent No. 5,013,556). This rejection is respectfully traversed.

A. The Invention

The present invention is described above. Dependent claim 7 includes the additional feature that the lipids for preparation of the liposomes comprise a lipid derivatized with a hydrophilic polymer.

B. The Cited Art

MEZEL is described above.

YAMAMOTO ET AL. is described above.

WOODLE ET AL. describe a liposome composition which contains between 1-20 mole percent of an amphipathic lipid derivatized with a polyalkylether. In one embodiment, the polyalkylether is polyethyleneglycol.

C. Analysis

According to M.P.E.P. §2142, one of the three requirements to establish a case of *prima facie* obviousness, is that the prior art references teach or suggest all the limitations of the claim.

Claim 1, from which claim 7 indirectly depends, includes the steps of "selecting a liposome size effective to inhibit precipitation of the compound from the supersatured solution when entrapped in the liposomes" and "forming liposomes having said selected size and which contain the supersatured solution of the compound."

As discussed above, Mezel teaches a multi-phase liposomal composition where the compound is present in solid form inside the liposomes (page 4, lines 16-20). In contrast, the present claims are directed to liposomes where the compound is entrapped in the form of a supersatured solution with no precipitate.

Yamamoto *et al.* nowhere teach the present claimed step of selecting a liposome size effective to inhibit precipitation of the compound from the supersatured solution when entrapped in the liposomes. In the liposomes of Yamamoto *et al.*, the compound is described as entrapped in a "supersatured state or in the form of solid or crystals" (page 2, lines 21-23). The present method provides a means to prepare liposomes having a supersatured solution of drug with no precipitate.

Thus, neither Mezel nor Yamamoto *et al.* show or suggest all of the steps of the present claims.

Woodle *et al.* is cited merely for the inclusion of lipids derivated with a hydrophilic polymer. Woodle *et al.* make no mention of entrapping a compound in a supersaturated solution form, without precipitation, due to selection of a liposome size effective to inhibit precipitation of the compound from the supersaturated solution.

Thus, the combined teachings of Mezel and Woodle *et al.* or Yamamoto *et al.* and Woodle *et al.* do not show or suggest every feature claimed. Accordingly, dependent claims 7 patentably defines over the teachings of Mezel or Yamamoto *et* al. in

combination with Woodle *et al.* Accordingly, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. §103.

V. Conclusion

In view of the foregoing, Applicants submits that the claims pending in the application are in condition for allowance. A Notice of Allowance is therefore respectfully requested.

If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 838-4310.

Respectfully submitted,

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